PHILIPPINE HEART ASSOCIATION
CLINICAL PRACTICE GUIDELINES
FOR THE MANAGEMENT OF CORONARY ARTERY DISEASE
(TECHNICAL WRITING GROUP)

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2008-2011

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PHA Clinical Practice Guidelines for the Management of Coronary Artery Disease

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INTRODUCTION

The groundwork for the Philippine Clinical Practice Guidelines (CPG) on Coronary Artery Disease (CAD) started in 1999 with the initiative of Dr. Isabelo Ongtengco as chair of the Council on Coronary Artery Disease. However, the CPG developed during that time was focused mainly on chronic stable angina pectoris (CSAP). When Dr. Myra Dolor-Torres chaired the Council in 2005, the scope of the CPG was expanded to include unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI), and ST-elevation myocardial infarction (STEMI).

Thereafter, the Council worked extensively in reviewing all the existing and current practice guidelines and appraisal of available scientific literature. The collated research material were reviewed and ... of directors of the Philippine Heart Association and training officers of accredited cardiology training institutions.

Majority of the statements in these guidelines reflect recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) guidelines as embodied in the following:

1. 2007 ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST Segment Elevation Myocardial Infarction
2. 2007 ACC/AHA Focused Update of the 2004 Guidelines for the Management of Patients with ST Segment Elevation Myocardial Infarction
3. 2007 ACC/AHA Focused Update of the 2002 Guidelines for the Management of Patients with Chronic Stable Angina
4. 2007 ACC/AHA Focused Update of the 2002 Guidelines for the Management of Patients with Chronic Stable Angina
5. 2007 ACC/AHA Focused Update of the 2005 Guideline Update for Percutaneous Coronary Intervention
6. 2004 ACC/AHA Guideline Update for CABG
7. 2008 ESC Guidelines for the Diagnosis and Treatment of Non-ST–Segment Elevation Acute Coronary Syndromes

Intended Users:

The PHA Clinical Practice Guidelines for the management of Coronary Artery Disease is intended for use by, but not exclusively for, cardiologists, internists, family medicine physicians, general practitioners and allied medical staff.
The statement “may be recommended” means that the procedure or treatment is useful or effective although with some conflicting evidence from other trials to trials conducted.

The statement “not recommended or contraindicated” means that the procedure is not useful or effective and may be harmful based on sufficient evidence from multiple/single, randomized/non randomized trial/s or meta-analyses.

Limitations and Future Directions:
These guidelines relied heavily on published foreign guidelines specifically from the ACC/AHA and ESC due to scarcity of large-scale local studies on coronary artery disease.

Expectedly, some recommendations may not be applicable in certain communities due to limited health resources. To address this challenge, some recommendations were modified to render them suitable to local practice.

The Coronary Artery Disease Council will create a task force to monitor the implementation of these clinical practice guidelines. This will hopefully provide meaningful research questions for future studies in the Philippines and answer some questions related to health outcomes and practices.

Introduction on Coronary Artery Disease
The global burden of ischemic heart disease is significant. In the Philippines, cardiovascular diseases ranked among the top 10 leading causes of morbidity, while both diseases of the heart and vascular system ranked 1st and 2nd in 2003, respectively for the leading causes of mortality.

Coronary artery disease (CAD) is commonly due to obstruction of the coronary arteries usually the epicardial arteries by atheromatous plaque. Obstructive CAD also has many non-atherosclerotic causes, including congenital abnormalities of the coronary arteries, myocardial bridging, coronary arteritis in association with the systemic vasculitides, and radiation-induced coronary disease. Myocardial ischemia may also occur in the absence of obstructive CAD, as in the case of aortic valve disease, hypertrophic cardiomyopathy, and idiopathic dilated cardiomyopathy.

Independent risk factors include a family history of premature coronary artery disease, cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, a sedentary lifestyle, and obesity. These risk factors accelerate or modify a complex and chronic inflammatory process that ultimately manifests as fibrous atherosclerotic plaque.

No uniform syndrome of signs and symptoms is initially seen in patients with CAD. Chest discomfort or angina pectoris is usually the predominant symptom. Adjectives frequently used to describe this distress include “viselike,” “constricting,” “suffocating,” “crushing,” “heavy,” and “squeezing.” In other patients, the quality of the sensation is more vague and described as a mild pressure-like discomfort, an
uncomfortable numb sensation, or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and usually occurs down the ulnar surface of the left arm; the right arm and the outer surfaces of both arms may also be involved. Epigastric discomfort alone or in association with chest pressure is not uncommon. Anginal discomfort above the mandible, below the epigastrium, or confined to the ear is rare.

Anginal “equivalents” (i.e., symptoms of myocardial ischemia other than angina), such as dyspnea, faintness, fatigue, and eructations are common, particularly in the elderly. A history of abnormal exertional dyspnea may be an early indicator of CAD even when angina is absent or no electrocardiographic (ECG) evidence of ischemic heart disease can be found. Dyspnea at rest or with exertion may be a manifestation of severe ischemia and lead to increases in left ventricular filling pressure. Nocturnal angina should raise the suspicion of sleep apnea.24

**Acute coronary syndromes**

Acute coronary syndromes are spectrum of clinical conditions ranging from unstable angina, non-ST elevation myocardial infarction (NSTEMI) to ST elevation AMI. Patients with ischemic discomfort may present with or without ST segment elevation in the ECG. Patients who present without ST segment elevation are either experiencing unstable angina or a NSTEMI. The distinction between these two diagnoses is ultimately made based on the presence or absence of a cardiac marker detected in the blood.

**Terminologies:**

- ACE-I: Angiotensin Converting Enzyme-Inhibitor
- ACS: Acute Coronary Syndromes
- ARB: Angiotensin Receptor Blocker
- AMI: Acute Myocardial Infarction
- CAD: Coronary Artery Disease
- CABG: Coronary Artery Bypass Graft Surgery
- CSAP: Chronic Stable Angina Pectoris
- ECG: Electrocardiogram
- LMWH: Low Molecular Weight Heparin
- LVEF: Left Ventricular Ejection Fraction
- NSTEMI: Non ST Elevation Myocardial Infarction
- PCI: Percutaneous Coronary Intervention
- STEMI: ST Elevation Myocardial Infarction
- TET: Treadmill Exercise Testing
- UA: Unstable Angina

**Summary of statements:**

- CSAP: 18 statements
- UA/NSTEMI: 23 Statements
- STEMI: 24 statements

Statement 9: Computed Tomographic (CT) Coronary Angiography
CT angiography may be recommended to diagnose CAD or rule out CAD in patients with a low-intermediate pretest probability of CAD or in patients with an equivocal or non-conclusive treadmill exercise or stress imaging test.

Statement 10: Invasive Coronary Angiography
Invasive coronary angiography is recommended in the following clinical circumstances:
1. Patients with known or possible angina pectoris who survived a sudden cardiac arrest or with serious ventricular arrhythmias
2. Severe stable angina with a high pretest probability of left main or three vessel CAD
3. Early recurrence of angina in post-revascularization patients
4. Patients with high risk criteria on noninvasive testing regardless of angina severity
5. Patients with an occupational requirement for a definitive diagnosis
6. Patients with an inconclusive diagnosis or inadequate prognostic information after noninvasive testing with intermediate to high risk of CAD
7. Patients who cannot undergo noninvasive testing due to disability, illness or morbid obesity
8. Patients who are being considered for major non-cardiac surgery, especially vascular surgery, with high risk features on noninvasive testing

Statement 11: Lifestyle Modification and Treatment of Coronary Disease Risk Factors
It is recommended that lifestyle modification and treatment of coronary disease risk factors be part of an optimal treatment strategy in patients with chronic stable angina.

Statement 12: Pharmacologic Therapy to Improve Prognosis
It is strongly recommended that patients with chronic stable angina receive the following medications to improve prognosis, thereby reducing the risk for myocardial infarction and death:
1. Aspirin
2. Statins
3. ACE – Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB)
4. Beta – Blockers post myocardial infarction

Statement 13: Pharmacologic Therapy to Reduce Angina
Anti-anginal drugs that may be substituted or added in descending order include:
1. Nitrates
2. Calcium channel blockers
3. Beta blockers
4. ACE inhibitors
5. Statins

Statement 1: History
A detailed history is the most essential part of the initial evaluation and remains the cornerstone in establishing the diagnosis of stable angina pectoris.

Statement 2: Physical Examination
A detailed physical examination should be done to identify or exclude other conditions associated with angina, evidence of non-coronary atherosclerotic disease, and other signs of co-morbid conditions.

Statement 3: Resting 12 lead ECG
It is recommended that a resting 12 lead ECG be recorded in all patients with symptoms suggestive of angina pectoris without an obvious non-cardiac cause of chest pain.

Statement 4: Laboratory tests
It is recommended that the following initial laboratory tests be performed to establish cardiovascular risk factors and associated conditions:
1. Fasting lipid profile, including total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides
2. Fasting glucose or oral glucose tolerance test or 2 hours postprandial glucose determination
3. Complete blood count
4. Creatinine
5. Markers of myocardial damage if clinical evaluation suggests an acute coronary syndrome

Statement 5: Chest X-Ray
It is recommended that chest x-ray (posteroanterior and lateral) be done in patients with signs or symptoms of congestive heart failure, valvular heart disease, aortic dissection/ aneurysm, pericardial disease, or pulmonary disease.

Statement 6: Echocardiography
Echocardiography is recommended in patients with clinically detected murmurs, history and ECG changes of prior MI and signs or symptoms of heart failure.

Statement 7: Treadmill Exercise Test
The treadmill exercise test (TET) is recommended as the initial test of choice to diagnose CAD and evaluate prognosis in patients with an intermediate pretest probability of CAD who have normal resting ECG and are able to exercise.

Statement 8: Stress Imaging Studies
Stress imaging studies are strongly recommended as the diagnostic and prognostic tests of choice in patients with resting ECG abnormalities, patients unable to exercise, and patients with previous revascularization (PCI or CABG).
I. Recommendations on Initial Patient Evaluation:

Statement 1: History

A detailed history is the most essential part of the initial evaluation and remains the cornerstone in establishing the diagnosis of stable angina pectoris.

A detailed description of the symptom of chest discomfort or pain enables the clinician to distinguish between typical angina, atypical angina, or non-cardiac chest pain. The characteristics of chest discomfort related to myocardial ischemia include five components: quality, location, duration of pain, factors that precipitate the pain, and factors that relieve the pain. Typical angina is usually described as pressure or heaviness, substernal in location, brief in duration, precipitated by exertion or emotional stress, and relieved by rest or sublingual nitrates. Non-cardiac chest pain lacks these qualities and implies a low probability of CAD. Non-cardiac causes of chest pain should be evaluated in such cases.

Although it may seem premature to predict the probability of CAD after the history, the clinico-pathological study done by Diamond and Forrester showed that it is possible to make a confident diagnosis on the basis of a detailed history alone. For example, a 60 year old man with typical angina was estimated to have a 90% probability of having significant CAD whereas a 25 year old woman with non-cardiac chest pain had a 1% probability of having CAD. Hence, the simple clinical observation of age, gender, and description of chest pain were found to be powerful predictors of the

Table 1: Canadian Cardiovascular Society Functional Classification of Angina Pectoris

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Specific Activity Scale</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Ordinary physical activity, (eg, walking and climbing stairs) does not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.</td>
<td>Play basketball, light jog (5 mph) without angina</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; when walking &gt; 2 blocks on level ground; or when climbing more than 1 flight of stairs at a normal pace and in normal conditions.</td>
<td>Ability to garden, rake, roller skate, walk at 4 mph on level ground, and have sexual intercourse without stopping</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of ordinary physical activity;</td>
<td>Ability to shower or dress</td>
</tr>
</tbody>
</table>
point to the presence of CAD risk factors. Signs of significant co-morbid conditions such as heart failure, anemia, diabetes, and renal insufficiency are important for risk stratification and treatment decisions. Physical examinations should also include an assessment of body mass index (BMI), waist circumference and waist to hip ratio to assist in evaluation of the metabolic syndrome.

Statement 3: 12 lead ECG

**It is recommended** that a resting 12 lead ECG be recorded in all patients with symptoms suggestive of angina pectoris without an obvious non-cardiac cause of chest pain.

A resting 12 lead ECG will be normal in greater than 50% of patients with stable angina. However, it should be emphasized that a normal resting ECG does not exclude the diagnosis of severe CAD.

ECG evidence of prior Q wave MI or ST-T wave changes consistent with myocardial ischemia favors the diagnosis of CAD and worsens the patient’s prognosis. The ECG may also show other abnormalities such as left ventricular hypertrophy, arrhythmias such as atrial fibrillation, bundle branch block, or other conduction defects which often occur in patients with multi-vessel CAD. These findings however lack specificity in the diagnosis of chronic stable angina since they are frequently caused by other types of cardiac disease.

There is little direct evidence to support routinely repeating the ECG at regular intervals unless there has been a change in symptoms or clinical status.

Statement 4: Laboratory test

**It is recommended** that the following initial laboratory tests be performed to establish cardiovascular risk factors and associated conditions

1. Fasting lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides)
2. Fasting glucose or oral glucose tolerance test or 2 hours postprandial glucose determination
3. Complete blood count
4. Creatinine
5. Markers of myocardial damage if clinical evaluation suggests an acute coronary syndrome

Fasting lipid profile and fasting plasma glucose should be evaluated to establish the patient’s risk profile and ascertain the need for treatment. There is no evidence to support recommendations on how regularly reevaluation should be done.
Consensus suggests annual measurement. However, patients with initial high levels of lipids or glucose should have measurements more frequently to determine efficacy of treatment.

The complete blood count, serum creatinine, and estimated creatinine clearance (by Cockcroft Gault formula) are also recommended at initial evaluation to add prognostic information. These tests, however, are not recommended as routine examinations during each subsequent evaluation.

If there is a clinical suspicion of an acute coronary syndrome, biochemical markers of myocardial damage such as troponin or creatine kinase MB by mass assay should be determined.

Statement 5: Chest X-Ray

It is RECOMMENDED that chest x-ray (posteroanterior and lateral) be done in patients with signs or symptoms of congestive heart failure, valvular heart disease, aortic dissection/ aneurysm, pericardial disease, or pulmonary disease.

The usefulness of the chest x-ray as a routine test in patients with stable angina is not well established. It does not provide specific information for diagnosis or for risk stratification. Hence, it should be requested in patients with the above conditions wherein abnormal findings are more likely.

Statement 6: Echocardiography

Echocardiography is RECOMMENDED in patients with clinically detected murmurs, history and ECG changes of prior MI and signs or symptoms of heart failure.

Most patients undergoing a diagnostic evaluation for stable angina do not need an echocardiogram. Echocardiography is useful to detect or rule out disorders such as valvular heart disease or hypertrophic cardiomyopathy in patients with clinically detected murmurs. Echocardiography also may be used to assess LV systolic and diastolic function in patients with a history or ECG findings of prior MI and symptoms or signs of heart failure. However, routine estimation of LV function is unnecessary for the diagnosis of stable angina pectoris. Echocardiography is not indicated in patients with suspected angina and a normal ECG, no history of MI, and no signs nor symptoms of heart failure.

II. Recommendations on Cardiac Tests for Diagnosis and Risk Stratification

Statement 7: Treadmill Exercise Test

The treadmill exercise test (TET) is RECOMMENDED as the initial test of choice to diagnose CAD and evaluate prognosis in patients with an intermediate pretest probability of CAD who have normal resting ECG and are able to exercise.

Because of its simplicity, lower cost, and widespread availability, the TET is the initial test of choice to identify inducible ischemia in the majority of patients with anormal resting ECG and is able to exercise. For patients with the following baseline ECG abnormalities: more than 1 mm of ST depression at rest, complete left bundle branch block, ECG criteria for LVH, pre-excitation (wolf-parkinson-white) syndrome, and electronically paced ventricular rhythm, exercise testing in combination with imaging should be the diagnostic test of choice. Patients unable to exercise should undergo pharmacological stress imaging studies.

It should be recognized that the treadmill exercise test should be performed only after a careful clinical evaluation of patients. It should not be carried out routinely in all patients. Furthermore, interpretation of treadmill exercise test findings requires a Bayesian approach to diagnosis. This approach uses clinicians’ pretest estimates of disease along with results of the treadmill test to generate individualized post-test probabilities of disease for a given patient.

Diagnostic testing is most valuable when the pre-test probability of obstructive CAD is intermediate. In this circumstance, the test result has the largest effect on the post-test probability of disease. A positive test result increases the likelihood of CAD whereas a negative test result decreases the likelihood. When the pretest probability of CAD is low, clinical judgment in such patients indicates that diagnostic work-up should focus on non-cardiac conditions. In contrast, when the probability of CAD is high, the treadmill test is less useful for the diagnosis of CAD since a positive test result only confirms the high probability of disease. Direct referral for diagnostic coronary angiography or, alternatively, stress imaging studies may be employed for diagnostic and prognostic assessment.

For diagnosis of CAD, horizontal or down-sloping ST segment depression greater than or equal to 1 mm or ST elevation for at least 60-80 msec after the end of the QRS complex, either during or after exercise, is used to define a positive test. Prognostic indicators include exercise capacity (measured by MET * level achieved), blood pressure and heart rate response to exercise, and the presence or absence of angina during the test.

*MET or metabolic equivalent is defined as resting oxygen consumption of 3.5mg/kg/min. The higher the METS achieved, the better the exercise capacity, i.e., METS of
Statement 8: Stress Imaging Studies

Stress imaging studies are STRONGLY RECOMMENDED as the diagnostic and prognostic tests of choice in patients with resting ECG abnormalities, patients unable to exercise, and patients with previous revascularization (PCI or CABG).

The most well-established stress imaging techniques are echocardiography and myocardial perfusion scintigraphy. Both may be used in combination with either exercise stress or pharmacological stress. A novel imaging modality, i.e. cardiac magnetic resonance (CMR), can be used in conjunction with dobutamine infusion to detect wall motion abnormalities or perfusion abnormalities induced by ischemia (Table 2).

Stress imaging techniques have several advantages over the conventional treadmill exercise test which include: superior diagnostic and prognostic performance due to the ability to quantify and localize areas of ischemia, the ability to provide diagnostic information in the presence of resting ECG abnormalities or inability of the patient to exercise, the ability to establish the functional significance of lesions in patients with angiographically confirmed coronary lesions, and the ability to demonstrate myocardial viability.

In general, stress echocardiography, stress myocardial perfusion imaging (MPI) and stress CMR have similar applications. The choice of which test to perform will depend on local facilities and expertise and cost-effectiveness considerations.

Because of its lower cost and generally greater probability and availability, stress echocardiography is more likely to be performed than stress MPI or stress CMR.

Table 2. A summary of comparative advantages of the various stress imaging techniques.

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Sensitivity%</th>
<th>Specificity%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress Echo (15)</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>Stress MPI (16)</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>Stress CMR (17,18)</td>
<td>87</td>
<td>80</td>
</tr>
</tbody>
</table>

Statement 9: Computed Tomographic (CT) Coronary Angiography

CT angiography MAY BE RECOMMENDED to diagnose CAD or rule out CAD in patients with a low-intermediate pretest probability of CAD or in patients with an equivocal or non-conclusive treadmill exercise or stress imaging test.

CT coronary angiography has emerged as a breakthrough noninvasive modality to diagnose coronary artery stenoses. The diagnostic performance of 4 slice CT and 16 slice CT to detect a significant coronary stenosis was remarkable with reported sensitivities between 66-91% and 72-95%, respectively, and specificities between 76-93% and 86-98% respectively. Therefore, the true diagnostic value of CT coronary angiography lies in its relatively high specificity. Because of the high negative predictive value, it can be used to exclude the presence of significant stenosis in patients with low pretest probability of CAD and in patients with equivocal stress tests.

Other clinical applications for CT coronary angiography that seem to be feasible according to current literature and evidence are as follows: the follow-up of patients with previous coronary artery bypass grafting, the follow-up of coronary stents when they are located in proximal branches, the evaluation of chronic total coronary occlusion before PCI, and evaluation of coronary artery anomalies.

Significant limitations are still present for CT angiography. Technical limitations in terms of spatial and temporal resolution, artifacts that exaggerate the severity of a stenosis, and contrast to noise ratio limit the reliability of this modality as an alternative to invasive coronary angiography. Also, patients with contraindications to intravenous iodinated contrast material (e.g. known allergy, impaired renal function or thyroid disorders) should be excluded from this procedure.

Statement 10: Invasive Coronary Angiography

Invasive coronary angiography IS RECOMMENDED in the following clinical circumstances:

1. Patients with known or possible angina pectoris who survived a sudden cardiac arrest or with serious ventricular arrhythmias
2. Severe stable angina with a high pretest probability of left main or three vessel CAD
3. Early recurrence of angina in post-revascularization patients
4. Patients with high risk criteria on noninvasive testing regardless of angina severity
5. Patients with an occupational requirement for a definitive diagnosis
6. Patients with an inconclusive diagnosis or inadequate prognostic information after noninvasive testing at intermediate to high risk of CAD
7. Patients who cannot undergo noninvasive testing due to disability, illness or morbid obesity
8. Patients who are being considered for major non-cardiac surgery, especially vascular surgery, with high risk features on noninvasive testing. Invasive coronary angiography remains the gold standard and most accurate technique for the diagnosis of obstructive CAD. It provides anatomical information on the severity of coronary lumen stenosis and enables the clinician to define therapeutic options (e.g., medical treatment or revascularization). However, coronary angiography is not a reliable indicator of the functional significance of a coronary stenosis and is insensitive in determining which plaques have characteristics likely to lead to acute coronary events. Nevertheless, the extent and severity of coronary disease identified on coronary angiography is one of the most powerful predictors of long term clinical outcome.  

III. Recommendations on Treatment

Statement 11: Lifestyle Modification and Treatment of Coronary Artery Disease Risk Factors

It IS RECOMMENDED that lifestyle modification and treatment of coronary disease risk factors be part of an optimal treatment strategy in patients with chronic stable angina.

General Objectives of Treatment:
The treatment of stable angina has two main objectives:
1. To improve prognosis by preventing myocardial infarction, heart failure progression, hospitalization, and death
2. To reduce or abolish symptoms of angina and heart failure

Treatment directed toward preventing myocardial infarction and death has the highest priority. For this objective, treatment measures that will reduce the incidence of acute thrombotic events, modify and retard progression of the atherosclerotic disease process, stabilize coronary plaques, and prevent development of left ventricular dysfunction are recommended.

It is also clinically important to address the second treatment objective since it is often of greater concern from the patient’s perspective. Efforts to reduce or abolish symptoms of angina will improve the physical function and quality of life of patients and consequently reduce hospitalizations for repeated attacks of angina.

Lifestyle changes, pharmacologic therapy and revascularization all have a role to play in improving prognosis and reducing symptoms of angina. The choice of therapy will depend on the patient’s risk profile, patient’s preference, and cost-effectiveness considerations.

Clinicians tend to focus on diagnostic and therapeutic interventions that are based on recent technological advances, often overlooking important aspects of high-quality care. Among these neglected areas is the counseling about lifestyle modification and treatment of coronary disease risk factors. Clinicians should have explicit discussions with their patients regarding the elements of lifestyle that could have contributed to their condition which include dietary habits, physical activity, and weight management. Likewise, it is essential that individual risk factors be reviewed with every patient. Particular attention should be placed on treatment of modifiable risk factors (e.g. smoking, hypertension, hypercholesterolemia) which have the greatest potential for reducing risk for myocardial infarction and death.

Statement 12: Pharmacologic Therapy to Improve Prognosis

It IS STRONGLY RECOMMENDED that patients with chronic stable angina receive the following medications to improve prognosis, thereby reducing the risk for myocardial infarction and death.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intervention and Goals</th>
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<tbody>
<tr>
<td>Smoking</td>
<td>Assess tobacco use; smoking cessation program</td>
</tr>
<tr>
<td>Elevated Cholesterol</td>
<td>Prescribe “Mediterranean” diet (e.g. fish, vegetables, fruits and poultry)</td>
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<tr>
<td></td>
<td>Consume foods rich in omega-3-fatty acids (e.g. EPA+DHA)</td>
</tr>
<tr>
<td></td>
<td>Increase physical activity (30-60 minutes of aerobic exercise 4 to 6 times a week)</td>
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<tr>
<td></td>
<td>Initiate statin therapy to achieve target LDL-cholesterol &lt;100mg/dl</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure control according to current JNC 7 guidelines</td>
</tr>
<tr>
<td></td>
<td>Goals: BP &lt; 140/90mmHg</td>
</tr>
<tr>
<td></td>
<td>BP&lt; 130/80 mmHg if with diabetes, heart failure, or renal insufficiency</td>
</tr>
<tr>
<td>Diabetes or Impaired</td>
<td>Blood sugar control with appropriate hypoglycemic therapy. Goal: Hba1c &lt;7%</td>
</tr>
<tr>
<td>Glucose Tolerance</td>
<td>Aggressive modification of other risk factors</td>
</tr>
<tr>
<td>Obesity</td>
<td>Weight management program (e.g. diet, increase physical activity). Initial goal should be weight loss of 10% from baseline Goals: BMI of 18.5 – 22.9 (Asians). Waist circumference of: &lt; 35 inches for men, &lt;31 inches for women</td>
</tr>
</tbody>
</table>
myocardial infarction and death:
1. Aspirin
2. Statins
3. ACE – Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB)
4. Beta – Blockers post myocardial infarction

Aspirin, low-dose (80-160 daily) remains the cornerstone of pharmacologic treatment to prevent coronary thrombosis. It acts via irreversible inhibition of cyclooxygenase thus reducing synthesis of platelet thromboxane A2. A meta-analysis of 287 randomized trials involving the use of aspirin in more than 3000 patients with stable angina showed a 33% reduction in the risk of adverse cardiovascular events. For patients who are allergic to aspirin, the thienopyridine clopidogrel may be considered as an alternative. Also, clopidogrel is given in addition to aspirin in patients after an acute coronary syndrome or post PCI with stenting. For patients with a history of gastrointestinal bleeding, aspirin in combination with a proton pump inhibitor may be used rather than clopidogrel. A recent study showed that the addition of esomeprazole to aspirin may be more cost effective than switching to clopidogrel for the prevention of recurrent ulcer bleeding.

Statin treatment should always be considered for patients with chronic stable angina. Statins lower LDL-cholesterol effectively, but anti-inflammatory and anti-thrombotic effects may contribute to the cardiovascular risk reduction. Secondary prevention studies indicate that the risk of atherosclerotic cardiovascular complications is reduced by at least 30% in patients with proven coronary artery disease. The dose of statin therapy may be increased as tolerated to achieve the desired LDL-cholesterol levels. Other lipid-lowering drugs may be used in combination with statins to control lipid levels in patients with severe dyslipidemia.

Niacin and fibrates may be useful, after LDL-cholesterol lowering, to reduce non-HDL-cholesterol. Only when TG levels are > 500 mg/dl may niacin or fibrates be used before statins to reduce the risk of pancreatitis.

ACE-I or ARBs are indicated for the treatment of patients with stable angina and co-existing hypertension, diabetes, heart failure, asymptomatic LV dysfunction and post-MI. In patients, without these co-existing conditions, ACE-I should still be given as secondary prevention treatment in all patients with proven coronary artery disease unless contraindicated. Two large randomized controlled trials e.g. HOPE 22 and EUROPA 23, showed that ramipril (10mg per day) and perindopril (8mg per day) reduced cardiovascular death, MI and stroke by 22% in high risk and intermediate risk CAD patients, respectively. It is of interest that both ramipril and perindopril are “tissue ACE-inhibitors” that has high lipophilicity and enzyme-binding capabilities. It has been postulated that ACE-I with these properties provide greater penetrance into the atherosclerotic plaque and more effective inhibition of tissue-ACE. Hence, there appears to be a particular mandate for the use of tissue-ACE-I because of their proven efficacy in providing cardiovascular protection. A large, randomized controlled trial called ONTARGET 24 has recently shown that the ARB, telmisartan, is non-inferior to ramipril in improving outcomes of patients at high risk of vascular events.

Aldosterone blockade may be combined with therapeutic doses of ACE-I or beta blockers in patients post-MI without significant renal dysfunction or hyperkalemia and have diabetes or LV dysfunction.

Beta-blockers have been shown in many randomized trials to reduce mortality by 30% in patients with prior MI with or without heart failure. It has been extrapolated that beta-blockers may also be beneficial in patients with stable angina without prior MI or heart failure. However, this hypothesis has not been proven in the few randomized controlled trials e.g. APSIS 25, ASIST 26, TIBET 27. These studies confirmed the beneficial anti-anginal effects of beta-blockers but did not show evidence of prognostic benefit. It should also be pointed out that beta-blockers with intrinsic sympathomimetic activity appeared to provide less cardiovascular protection regarding mortality after an acute MI.

Statement 13: Pharmacologic Therapy to Reduce Angina

It IS RECOMMENDED that a beta-blocker be used as initial therapy to reduce symptoms of angina

Anti-anginal drugs that may be substituted or added in descending order of preference include:
1. Calcium channel blocker
2. Long-acting nitrates
3. Nicorandil
4. Ivabradine
5. Trimetazidine

The most commonly used anti-anginal drugs are beta-blockers, calcium channel blockers and nitrates. These drugs are effective in reducing symptoms of angina by reducing myocardial oxygen demand and increasing blood flow to the ischemic area.

Beta-blockers should be strongly considered as initial anti-anginal treatment for patients with chronic stable angina on the basis of their prognostic benefit in post-MI patients. All beta-blockers appear to be effective in reducing symptoms but beta-1
selective agents (e.g. metoprolol, bisoprolol, and atenolol) are preferred due to lesser adverse effects. It has been conventional to adjust the dose of beta-blockers to reduce heart rate at rest to 55 to 60 beats per minute.

Calcium-channel blockers (CCB) are generally as effective as beta-blockers in relieving angina as shown in randomized trials comparing CCB and beta-blockers (e.g. APSIS 25, ASIIST 26, TIBET 27, IMAGE 28, TIBBS 29). The clinical effectiveness of CCBs as anti-anginal treatment was evident with the non-dihydropyridine drugs (e.g. amiodipine and felodipine). Hence, in the absence of prior MI, the choice between a beta-blocker and a CCB may be guided by the patient’s preference and tolerance to adverse effects.

Long-acting nitrates are equally as effective as beta-blockers or CCB in reducing symptoms of patients with exertional stable angina. However, there is no documentation of the prognostic benefit of monotherapy with nitrates in patients with stable angina. Generally, the studies showed greater reduction in symptoms and improved exercise tolerance when nitrates are developmental of nitrate tolerance; hence, patients should have a “nitrate-free” interval each day to preserve its anti-anginal effects.

Nicorandil is a potassium channel activator with nitrate-like effects and cardioprotective properties. The IONA trial 30 showed a non-significant risk reduction in non-fatal MI and cardiac death during 1.6 years of treatment with nicorandil as add-on therapy to conventional drugs. However, there was significant reduction of hospital admissions for cardiac chest pain.

Trimetazidine, a metabolic agent with anti-anginal properties, has a different mechanism of action from the conventional anti-anginal therapy (e.g. beta-blockers, CCB, nitrates). It lessens ischemic injury and improves cardiac performance during ischemia through reduction in fatty acid oxidation and stimulation of glucose oxidation. Its anti-anginal efficacy has been documented in numerous small randomized trials in monotherapy or in combination with conventional hemodynamic drugs. Recent studies have shown that trimetazidine also proved to be effective in relieving angina in patients with recurrent angina after a revascularization procedure and despite treatment with metoprolol. In patients with ischemic cardiomyopathy, trimetazidine

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### Table 4. Lesions adverse characteristic scoring (SYNTAX Score)

<table>
<thead>
<tr>
<th>Diameter reduction*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Total occlusion</td>
<td>x5</td>
</tr>
<tr>
<td>- Significant lesion (50-99%)</td>
<td>x2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total occlusion (TO)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age &gt;3months or unknown</td>
<td>+1</td>
</tr>
<tr>
<td>- Blunt stump</td>
<td>+1</td>
</tr>
<tr>
<td>- Bridging</td>
<td>+1</td>
</tr>
<tr>
<td>- First segment visible beyond TO</td>
<td>+1/ per non-visible segment</td>
</tr>
<tr>
<td>- Side branch (SB) - Yes, SB &lt; 1.5mm**</td>
<td>+1</td>
</tr>
<tr>
<td>- Yes, both SB &lt; &amp; e” 1.5mm</td>
<td>+1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trifurcations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1 diseased segment</td>
<td>+3</td>
</tr>
<tr>
<td>- 2 diseased segments</td>
<td>+4</td>
</tr>
<tr>
<td>- 3 diseased segments</td>
<td>+5</td>
</tr>
<tr>
<td>- 4 diseased segments</td>
<td>+6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bifurcations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Type A, B, C</td>
<td>+1</td>
</tr>
<tr>
<td>- Type D, E, F, G</td>
<td>+2</td>
</tr>
<tr>
<td>- Angulation &lt;70°</td>
<td>+1</td>
</tr>
</tbody>
</table>

| Aorto ostial stenosis | +1  |
| Severe tortuosity     | +2  |
| Length > 20mm         | +1  |
| Heavy calcification   | +2  |
| Thrombus              | +1  |

| *Diffuse disease*/small vessels | +1/ per segment number  |

---

* In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50-99% luminal diameter reduction) or occlusive.

** If all the side branches are 1.5mm in diameter, no points are added since the lesion is considered as a bifurcation and it will be scored as such.

risk factor modification should be undertaken before therapy is considered a failure. Optimal medical therapy includes treatment with aspirin, statin, ACE-inhibitors and beta-blockers or any anti-anginal drug as well as risk factor modification. In general, patients with persistent class III – IV symptoms warrant consideration for revascularization.

Statement 15: Revascularization with Percutaneous Coronary Intervention (PCI)

Percutaneous coronary intervention IS RECOMMENDED for relief of angina symptoms in patients without high-risk coronary anatomy and in whom procedure risks do not outweigh potential benefits.

Evidence from randomized trials suggests that PCI may be considered as an effective option for relief of angina as long as SYNTAX scores are 32 or less (see Table 4).

PCI does not eliminate the need for medical therapy. As such, medical therapy should be continued aggressively after PCI. While PCI does not provide survival benefit in stable angina, it is more effective than medical treatment in reducing events that impair quality of life.

The advantages of PCI include a low procedure-related morbidity and mortality in properly selected patients, a short hospital stay and early return to activity. The disadvantages of PCI include possible acute coronary occlusion, restenosis, and possibility of incomplete revascularization. Despite these disadvantages, PCI remains a useful primary strategy or alternative to surgery and its efficacy has extended to more complex lesions over the past decade.

*High risk coronary anatomy (HRCA) is defined as > 50% stenosis for Left main coronary artery and/or significant 3-vessel coronary artery disease > 70% stenosis and a SYNTAX Score of 33 or higher (see table 4).

Statement 16: Revascularization with Coronary Artery Bypass Graft Surgery (CABG)

CABG IS RECOMMENDED in the following subset of patients based on evidence of prognostic benefit:

1. Significant left main coronary disease
2. High Risk Coronary anatomy that is not suitable for PCI
3. Severe proximal stenosis of 3 major coronary arteries and severe stenosis of two major coronary arteries, including high-grade stenosis of the proximal left anterior descending artery in patients with high SYNTAX scores (Table 4)

For most patients, the goal of treatment should be complete or near-complete elimination of angina chest pain and a return to normal activities and functional capacity (CCS class 1). This goal should be accomplished with minimal side effects of therapy. Also, coexisting medical conditions may affect the selection of anti-anginal treatment, e.g. nitrates are contraindicated in patients with aortic valve stenosis or hypertrophic obstructive cardiomyopathy.

Hence, despite the array of anti-anginal treatment, the choice of which drug to prescribe should be tailored to the needs of the individual patient, and its efficacy should be monitored carefully. Generally, the dosing of one drug should be optimized before adding a second or third drug.

Statement 14: Indication for Revascularization

Revascularization IS RECOMMENDED in the following subset of patients:

1. High-risk patients known to benefit from revascularization (e.g. significant left main disease, severe 3 vessel disease, left ventricular dysfunction, high risk features on non-invasive imaging)
2. Patients with technically suitable coronary anatomy who do not respond adequately to optimal medical therapy and who wish to remain physically active

There are currently two well-established revascularization approaches: Coronary Artery Bypass Graft Surgery (CABG) and Percutaneous Coronary Intervention (PCI). The selection of the method of revascularization should be based on the likelihood of success and the risk of peri-procedural morbidity and mortality.

Patients with high-risk coronary anatomy and those with left ventricular dysfunction have been shown to have a better prognosis with surgery than with medical treatment. Outside the high-risk population, an initial pharmacologic approach with intensive reduced ischemic attacks not only clinically but objectively as seen in improvement of gated SPECT myocardial perfusion images. Whether trimetazidine will influence the prognosis of patients with stable angina has yet to be determined.

Ivabradine, the most novel anti-anginal drug to date, is a selective and specific sinus node inhibitor with chronotrophic effects both at rest and during exercise without affecting contractility. It may be used as an alternative agent in patients who do not tolerate beta-blockers or in patients with CAD and left ventricular dysfunction. A recent large-scale randomized trial called BEAUTIFUL showed that pure heart rate reduction with ivabradine is associated with lower hospitalization rates for heart failure but with no significant reduction in total mortality.
Analysis of large randomized trials (e.g. Coronary Artery Surgery Study [CASS], Veterans Administration Cooperative Study [VA study], and European Coronary Surgery Study [ECSS]) has revealed that the subset of patients with a specific coronary anatomy, as mentioned above, had better survival with coronary bypass surgery than with medical treatment. Significant stenosis was defined as > 70% of major coronary arteries or > 50% of the left main stem. The presence of impaired LV function (ejection fraction less than 50%) increased the survival benefit of surgery over medical treatment.

Coronary bypass surgery has also consistently reduced the symptoms of patients with chronic stable angina in large observational studies. However, the advantage for the group treated with surgery became less after 10 post-operative years which was related to late vein graft failure. It is important to note that these trials were performed in the relatively early years of bypass surgery, and outcomes have improved over time.

The first randomized controlled clinical trial to compare PCI using a drug-eluting stent to CABG in patients with left main disease and three vessel disease is the Syntax trial which enrolled 1800 patients. Results showed that the rates of major adverse cardiac events (MACE) or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; \(P=0.002\)), in large part because of an increased rate of repeat revascularization (13.5% vs. 5.9%, \(P<0.001\)). Therefore, the noninferiority of PCI as compared with CABG was not demonstrated. However, outcome in the trial’s secondary endpoint (the combined rate of all-cause death, stroke and MI, with revascularization removed) was almost similar (7.6% for PCI and 7.7% for CABG \(p=0.98\)) in large part due to the increase in stroke rate with CABG (2.2%, vs. 0.6% with PCI).  

Patients who require revascularization should be stratified according to feasibility of PCI versus CABG using the SYNTAX scoring system. For patients with a SYNTAX score of 32 or less, the MACE rate appears comparable for both PCI and CABG. However, for patients whose SYNTAX score is 33 or higher, PCI plays no role in the patients’ management. The likelihood of full revascularization in this latter group of patients is small. Therefore the patient should be considered for PCI only if the patient is deemed a high risk candidate for CABG due to other co-morbid conditions or unless the patient refuses CABG. Choosing CABG (over PCI) implies a roughly 8-per-100 lower probability of needing another procedure during the ensuing year, at the expense of a roughly 2-per-100 higher risk for stroke, and longer recuperation time after CABG than after stenting. On the other hand, higher rate of revascularization and need for prolonged dual anti-platelet therapy with drug-eluting stents should be discussed as well.

Statement 17: Non Conventional Treatment: Chelation Therapy

Chelation therapy IS NOT RECOMMENDED and maybe harmful to patients with CAD.

Chelation therapy consists of a series of intravenous infusion containing ethylene diamine tetra acetic acid (EDTA) in combination with other substances. EDTA is water soluble and chelates metallic ions from the blood. At normal pH, EDTA binds these dissolved metals, in decreasing order of strength, is iron, mercury, copper, aluminum, nickel, lead, cobalt, zinc, cadmium, manganese, magnesium, and calcium. Proponents believe that it is effective against atherosclerosis as removing calcium will lead to softening of hardened arteries. Based on extensive reviews conducted by PHA Council of CAD in year 2005, the group found no scientific evidence that chelation therapy is beneficial in treating patients with atherosclerotic heart disease and peripheral vascular disease. Additionally, using this form of unproven treatment may deprive patients of receiving the well established treatment modalities of proven efficacy. Furthermore, chelation therapy is expensive and is not devoid of side effects. Cases of renal failure and depletion of mineral contents has been reported.

IV. Recommendations on Follow-up

Statement 18: Recommendations on Follow-up

It IS RECOMMENDED that follow-up tests should be done in patients with worsening of angina or development of co-morbid conditions despite optimal medical therapy and/or revascularization. Follow-up of success of treatment includes an assessment of:
1. Relief or worsening of angina
2. Improvement of level of activity
3. Success in risk factor modification
4. Development of co-morbid conditions
5. Decrease in ischemic burden by non-invasive testing such as stress imaging,
V. Algorithm

![Algorithm Diagram]

* Intermediate or high probability of CAD: presence of risk factors for CAD i.e. older, male gender, smoking, family history of premature CAD, hypertension, diabetes mellitus, hyperlipidemia, obesity, sedentary lifestyle

† Treadmill exercise testing, Stress Imaging Studies i.e. stress echocardiography, stress myocardial imaging studies and stress cardiac magnetic resonance

VI. References


(3) Diamond GA and Forrester JS. Probability of CAD. Circ 1982; 65:641-642


(29) TIBBS: Total Ischemic Burden Bisoprolol Study. Von Armin T. Medical treatment to reduce total ischemic burden: Total Ischemic Burden Bisoprolol Study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. J Am Coll Cardiol 1995;25:231-38


It IS RECOMMENDED that the following management strategies should be instituted:
1. Bed rest with continuous ECG monitoring for ischemic and arrhythmia detection in patients with ongoing rest pain.
2. Supplemental oxygen should be administered to patients with UA/NSTEMI for patients with cyanosis or respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (SaO2 greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia.

Statement 8: Nitrates
It IS RECOMMENDED that nitrates (sublingual tablet or spray), followed by intravenous administration, be administered for the immediate relief of ischemic and associated symptoms.

Statement 9: Beta blockers
It IS RECOMMENDED that beta-blocker by oral or IV route be administered if there is ongoing chest pain in the absence of contraindications.

Statement 10: Calcium channel blockers:
It MAY BE RECOMMENDED to use oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindication and when beta-blockers and nitrates are maximally used.

Statement 11: Angiotensin Converting Enzymes Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB):
An ACE-I/ARB IS RECOMMENDED when hypertension persists despite treatment with nitroglycerin (NTG) and a beta-blocker in patients with LV systolic dysfunction or congestive heart failure (CHF), high risk chronic CAD, in post ACS (with or without) diabetes, and in chronic kidney disease (CKD) unless contraindicated.

Statement 12: Morphine Sulfate
It IS RECOMMENDED that morphine sulfate be administered intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation are present.

Statement 13: Aspirin
It IS STRONGLY RECOMMENDED that aspirin at initial dose of 160-325 mg non-enteric formulation, followed by 80-160 mg daily be administered as soon as possible after presentation and continued indefinitely.

Statement 14: ADP receptor antagonists (Clopidogrel, ticlopidine)
It IS STRONGLY RECOMMENDED
Statement 15: Anticoagulants (Heparins)
It IS STRONGLY RECOMMENDED that anticoagulation with subcutaneous enoxaparine or intravenous unfractioned heparin (UFH) should be added to antiplatelet therapy with ASA and/or clopidogrel.

Statement 16: Glycoprotein IibIIa inhibitors
It IS RECOMMENDED to use glycoprotein IibIIa inhibitors (tirofiban) in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is not planned; or inpatients undergoing PCI with or without clopidogrel administration.

Statement 17: Factor X inhibitor:
It IS RECOMMENDED to use fondaparinux, in lieu of enoxaparine, at a dose of 2.5 mg SC once daily in whom a conservative strategy is selected and who have an increased risk of bleeding.

Statement 18: Fibrinolytic therapy
It IS NOT RECOMMENDED to use intravenous fibrinolytic therapy in patients with UA or in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block (LBBB).

Statement 19: Early Conservative versus Invasive Strategies
It IS RECOMMENDED that an early invasive strategy (as early as possible up to 72 hours) followed by revascularization (PCI or CABG) with any of the following high-risk indicators:

a) Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
b) Elevated cardiac biomarkers (TnT or TnI)
c) New or presumably new ST-segment depression
d) Intensive lipid-lowering therapy is strongly recommended by combining dietary interventions with pharmacotherapy by statins, or combining with other lipid-lowering agents to reduce LDLc < 100 mg/dL. Further reduction to less than 70 mg per dL may be recommended.

e) Hemodynamic instability
f) Sustained ventricular tachycardia
g) PCI within 6 months
h) Prior CABG
i) High-risk score (e.g., TIMI, GRACE)

Statement 20: Coronary angiography
It IS NOT RECOMMENDED in patients with extensive co-morbidities (e.g. liver or pulmonary failure, cancer), in whom the risks of revascularization are not likely to outweigh the benefits or in patients with acute chest pain and a low likelihood of ACS or in patients who will not consent to revascularization regardless of the findings.

Statement 21: Percutaneous coronary intervention (PCI)
An early invasive PCI strategy IS RECOMMENDED for patients with UA/NSTEMI who have no serious co-morbidities and who have coronary lesions amenable to PCI and any of the high-risk features.

PCI (or CABG) is also recommended for UA/NSTEMI patients with 1-2 vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high risk criteria on non invasive testing.

Statement 22: Coronary artery bypass graft (CABG) surgery
CABG IS RECOMMENDED for patients with significant left main disease and the preferred revascularization strategy for patients with multi-vessel coronary disease, with depressed systolic function (LVEF < 50%), and diabetes.

Statement 23: It IS RECOMMENDED that the following specific instructions should be given:
a. Lifestyle modification that includes smoking cessation, achievement or maintenance of optimal weight, daily exercise, and diet.
b. Daily exercise of 30 minutes or 5 days per week.
c. Consider referral of patients who are smokers to smoking cessation program or clinic and/or an out-patient cardiac rehabilitation program.
d. Intensive lipid-lowering therapy is strongly recommended by combining dietary interventions with pharmacotherapy using statins, or combining with other lipid-lowering agents to reduce LDLc < 100 mg/dL. Further reduction to less than 70 mg per dL may be recommended.
e. A fibrate or niacin if high-density lipoprotein (HDL) cholesterol is less than 40 mg per dL, occurring as an isolated finding or in combination with other lipid abnormalities.
f. Hypertension control to a blood pressure of less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease.
g. Tight control of hyperglycemia in diabetes. Goal is HbA1c of less than 7%.
h. Antiplatelet Agents/ Anticoagulants (see page 54)
I. Introduction:

Non-ST elevation myocardial infarction (NSTEMI) is defined as condition where there is no ST elevation on ECG but with elevation of cardiac enzymes. On the other hand, unstable angina (UA) is not associated with ST elevation or cardiac enzymes elevation but with ECG ST or T wave changes coupled with typical anginal pains. It is important to differentiate these above-mentioned conditions since prognosis and management can differ. For example, acute reperfusion therapy or thrombolysis is a contraindication for ACS patients without ST-segment elevation.

II. Diagnosis and Risk Assessment

Patients with a high likelihood of ischemia due to CAD are at a greater risk of an untoward cardiac event than are patients with a lower likelihood of CAD. Therefore, an assessment of the likelihood of CAD is the starting point for the determination of prognosis in patients who present with symptoms suggestive of an ACS.

Statement 1: Diagnosis and Risk Assessment

Patients with the following symptoms and signs require immediate assessment for the initiation of the ACS protocol:
- Chest pain or severe epigastric pain, non-traumatic in origin, with component typical of myocardial ischemia or MI: Central/substernal compression or crushing chest pain pressure, tightness, heaviness, cramping, burning, aching sensation
- Unexplained indigestion, belching, epigastric pain
- Radiating pain in neck, jaw, shoulders, back, or 1 or both arms
- Associated dyspnea
- Associated nausea and/or vomiting
- Associated diaphoresis

The clinical presentation of patients with unstable angina and non ST elevation MI present itself in variety of symptoms. However, the frequent and typical manifestations would be the following:
- Prolonged (>20 min) anginal pain at rest
- New onset severe angina
- Crescendo/Accelerated Angina
- Post MI angina

Statement 2: Electrocardiogram:

It IS STRONGLY RECOMMENDED that a 12 lead ECG be obtained immediately within 10 minutes of emergency room (ER) presentation in patients with ongoing chest discomfort.

If the initial ECG is not diagnostic, but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs, initially at 15-30 min intervals, should be performed to detect the potential for development of ST segment elevation or depression.

The ECG is critical not only to add support to the clinical suspicion of CAD but also to provide prognostic information that is based on the pattern and magnitude of the abnormalities. Importantly, transient ST-segment changes (greater than or equal to 0.05 mV) that develop during a symptomatic episode at rest and that resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD.

Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the 2 diagnosis is based ultimately on the detection in the blood of markers of myocardial necrosis. 1,2

Statement 3: Treadmill Exercise Test

It IS NOT RECOMMENDED to perform stress test within 48 hours of the last chest pain

In patients who continue to have typical chest pain, stress test should not be performed. However, stress test has be used as a predictive tool of prognosis in patients with non-diagnostic ECG provided there is no chest pain, no signs of heart failure and normal cardiac markers on repeat examination. 3

Statement 4: Biomarkers of Cardiac Injury

It IS STRONGLY RECOMMENDED that troponin be measured in all patients with chest discomfort consistent with ACS. In patients with negative cardiac markers within 6 hours of the onset of pain, another sample should be drawn in the time frame 8-12 after symptom onset.

cTNT or cTNI are the preferred markers of myocardial injury because they are more specific and more sensitive than the traditional cardiac enzymes such as creatinine
kerase (CK) or its isoenzyme MB (CKMB). Additionally, troponins are the best biomarker to predict short term (<30 days) outcome with respect to MI and death. 4, 5, 6 In patients with AMI, an initial rise in troponins in peripheral blood occurs after 3-4 hours. Troponin levels may persist for up to 2 weeks. In NSTEMI, minor elevation of troponins may be measurable only over 48-72 hours. The high sensitivity of troponin tests allows the detection of myocardial damage undetected by CKMB in up to one third of patients. With currently available assays, cTnI and cTnT are of equal sensitivity and specificity in the detection of cardiac damage. 7 The choice should be made on the basis of cost and the availability of instrumentation at the institution.

A single negative test for troponins on arrival of the patient in hospital is not sufficient for ruling out an ACS. Repeated blood sampling and measurements are required 6-12 hours after admission and after any further episodes of severe chest pains.

**Statement 5: Other Biomarkers:**

It **IS NOT RECOMMENDED** to request for Total CK (without MB), AST, SGOT, beta hydroxybutyric dehydrogenase, and/or lactate dehydrogenase (LDH) as markers for the detection of cardiac injury.

**Statement 6: Risk Stratification**

It **IS RECOMMENDED** for patients who present with chest discomfort or other ischemic symptom to undergo early risk stratification for risk of cardiovascular events (e.g. death or MI) based on an integration of the patient’s history, physical examination, ECG findings and result of cardiac biomarkers.

Early risk stratification is useful in 1) selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting) and 2) selection of therapy, including platelet glycoprotein (GP) IIb/IIIa inhibitors and invasive management strategy. A number of risk assessment tools have been developed in assessing risk of death and ischemic events; these are the Thrombolysis in Myocardial infarction (TIMI) risk score 8, Platelet Glycoprotein IIb-IIIa in Unstable Angina (PURSUIT) risk model 9, and the Global Registry of Acute Coronary Events (GRACE) risk model (see figure 1) 10,11 (see Table 1 for comparison of these 3 risk models).

---

**Figure 1. GRACE Prediction Score Card and Nomogram for All-Cause Mortality from Discharge to 6 Months**

**Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome**

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the local score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

### Table 1: Comparison of Risk Models

<table>
<thead>
<tr>
<th>Risk Model</th>
<th>Points</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI</td>
<td>2.0-6.0</td>
<td>0.50-0.95</td>
<td>0.20-0.80</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>2.0-6.0</td>
<td>0.50-0.95</td>
<td>0.20-0.80</td>
</tr>
<tr>
<td>GRACE</td>
<td>0-100</td>
<td>0.60-0.95</td>
<td>0.10-0.70</td>
</tr>
</tbody>
</table>

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Table 1: Comparison of three known risk models used in the assessment of risk of death and myocardial infarction in patients with NSTEMI and UA

<table>
<thead>
<tr>
<th>TIMI risk score (7 variables)</th>
<th>PURSUIT risk model (6 variables)†</th>
<th>GRACE risk model (8 variables)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 years or older</td>
<td>age</td>
<td>older age</td>
</tr>
<tr>
<td>at least 3 risk factors for CAD</td>
<td>heart rate</td>
<td>heart rate</td>
</tr>
<tr>
<td>prior coronary stenosis of 50% or more</td>
<td>systolic blood pressure</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>ST-segment deviation on ECG presentation</td>
<td>ST-segment depression</td>
<td></td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>signs of heart failure</td>
<td>Killip classification</td>
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<tr>
<td>at least 2 anginal events in prior 24 hours</td>
<td>cardiac enzymes</td>
<td>cardiac enzymes</td>
</tr>
<tr>
<td>elevated serum cardiac biomarkers</td>
<td>cardiac enzymes</td>
<td>serum creatinine level</td>
</tr>
<tr>
<td>use of aspirin in prior 7 days</td>
<td></td>
<td>Cardiac arrest at hospital arrival</td>
</tr>
</tbody>
</table>


In the PURSUIT risk model, critical clinical features associated with an increased 30-day incidence of death and the composite of death or myocardial (re)infarction were (in order of strength) age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure (HF), and cardiac enzymes. In the GRACE risk model, the 8 variables used are older age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac markers, and heart rate. The sum of scores is applied to a reference nonogram to determine the corresponding all-cause mortality from hospital discharge to 6 months (see figure 1). Any of these risk scores or models can be used to assess risk of death and myocardial infarction in patients with NSTEMI and UA.

III. Hospital Care:

Statement 7: General Recommendations on Initial Management:

It IS RECOMMENDED that the following management strategies should be instituted:

1. Bed rest with continuous ECG monitoring for ischemic and arrhythmia detection in patients with ongoing rest pain.
2. Supplemental oxygen should be administered to patients with UA/NSTEMI for patients with cyanosis or respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (SaO₂ greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia.
Statement 8: Nitrates

It IS RECOMMENDED that nitrates (sublingual tablet or spray), followed by intravenous administration, be administered for the immediate relief of ischemic and associated symptoms.

For initial management of anginal pains, three 0.4mg sublingual NTG tablets or spray taken 5 min apart can be administered. If symptoms are not relieved, intravenous NTG may be initiated at a rate of 10mcg/min through continuous infusion with non-absorbing tubing and increased by 10 mcg per min every 3 to 5 min until some symptom or blood pressure response is noted. Caution should be used when systolic blood pressure falls to less than 110 mm Hg in previously normotensive patients or greater than 25% below the starting mean arterial blood pressure if hypertension was present. Although recommendations for a maximum dose are not available, a ceiling of 200 mcg per min is commonly used. When patients have been free of pain and other manifestations of ischemia for 12 to 24 h, an attempt should be made to reduce the dose of intravenous NTG and to switch to oral or topical nitrates (see table 3 for list of anti-anginal drugs).

Table 3: NTG and Nitrates that are locally available:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dose/Dosage</th>
<th>Duration of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>Sublingual tablets</td>
<td>0.3-0.6 mg up to 1.5 mg</td>
<td>1-7 mins</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.4 mg as needed</td>
<td>similar to SL tablets</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.2-0.8 mg/h every 12h</td>
<td>8-12 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>5-200 mg/min</td>
<td>Tolerance in 7-8 h</td>
</tr>
<tr>
<td>Isosorbide Dinitrate</td>
<td>Oral</td>
<td>5-80 mg, 2 or 3 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td></td>
<td>Oral, slow release</td>
<td>40 mg 1 or 2 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>20 mg twice daily</td>
<td>12-24 h</td>
</tr>
<tr>
<td></td>
<td>Oral, slow release</td>
<td>60-240 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

It is not recommended to administer NTG or other nitrate within 24 h of sildenafil use. Sildenafil inhibits the phosphodiesterase (PDE5) that degrades cyclic guanosine monophosphate (cGMP), and cGMP mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-mediated vasodilation is markedly exaggerated and prolonged in the presence of sildenafil. Nitrate use within 24 h after sildenafil or the administration of sildenafil in a patient who has received a nitrate within 24 h has been associated with profound hypotension, MI, and even death. 12

Statement 9: Beta blockers

It IS RECOMMENDED that beta-blocker by oral or IV route be administered if there is ongoing chest pain in the absence of contraindications.

Beta-blockers competitively block the effects of catecholamines on cell membrane beta-receptors. Beta-blockers should be started early in the absence of contraindications. These agents should be administered IV (the only locally available IV beta blocker is esmolol) followed by oral administration in high-risk patients as well as in patients with ongoing rest pain or orally for intermediate-and low-risk patients (see table 4 on different beta blocker drugs).

Table 4 List of Beta-Blockers in Clinical Use that is locally available.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose for Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>20-80 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50-200 mg twice daily</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-200 mg/d</td>
</tr>
<tr>
<td>Timolol</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Esmolol (intravenous)</td>
<td>50-300 mcg . kg⁻¹ . min⁻¹</td>
</tr>
<tr>
<td>Pindolol</td>
<td>2.5-7.5 mg 3 times daily</td>
</tr>
</tbody>
</table>

Beta-blockers are contraindicated in the setting of continuing or frequently recurring ischemia, a non-dihydropyridine calcium antagonist (e.g. verapamil or diltiazem) may be administered as initial therapy in the absence of severe LV dysfunction or other contraindications.

Statement 10: Calcium channel blockers:

It MAY BE RECOMMENDED to use oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindication and when beta-blockers and nitrates are maximally used.

Definitive evidence for benefit with all calcium antagonists in UA is predominantly limited to symptom control. Rapid-release, short-acting dihydropyridines (e.g. nifedipine) must be avoided in the absence of adequate concurrent beta-blockade in ACS because controlled trials suggest increased adverse outcomes. 13, 14, 15 Verapamil and diltiazem should be avoided in patients with pulmonary edema or
dysfunction. \textsuperscript{16} Amlodipine and felodipine, however, appear to be well tolerated by patients with chronic LV dysfunction. \textsuperscript{17} (see table 5 on different listing of calcium channel blockers)

Table 5: List of Calcium Antagonists in Clinical Use that is locally available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate release; 30-90 mg daily orally</td>
</tr>
<tr>
<td></td>
<td>Slow release: 30-180 mg orally</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Isradipine</td>
<td>2.5-10 mg twice daily</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-40 mg 3 times daily</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Immediate release: 30-80 mg 4 times daily</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-320 mg once daily</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Immediate release: 80-160 mg 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-480 mg once daily</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release: 80-160 mg 3 times daily</td>
</tr>
</tbody>
</table>

The administration of the following treatment strategies can be done but with caution:

1. Extended-release form of non-dihydropyridine calcium antagonists instead of a beta-blocker
2. Immediate-release dihydropyridine calcium antagonists in the presence of a beta-blocker.

However, it is not recommended to administer immediate-release dihydropyridine calcium antagonists in the absence of a beta-blocker.

Statement 11: Angiotensin Converting Enzymes Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB):

An ACE-I/ARB \textbf{IS RECOMMENDED} when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or congestive heart failure (CHF), high risk chronic CAD, in ACS patients with diabetes, and in chronic kidney disease (CKD) unless contraindicated.

ACE-Is have been shown to reduce mortality rate in patients with AMI or who recently had an MI and have LV systolic dysfunction. \textsuperscript{18-21} in diabetic patients with LV dysfunction. \textsuperscript{22} and in a broad spectrum of patients with high-risk chronic CAD, including patients with normal LV function

An ACE-I is recommended for all post-ACS patients. ARBs should also be considered in patients who are intolerant to ACE-I and/or who have heart failure or MI with LVEF<40%.

Statement 12: Morphine Sulfate

It \textbf{IS RECOMMENDED} that morphine sulfate be administered intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation are present.

Morphine sulfate 1 to 5 mg intravenously (IV) is recommended for patients whose symptoms are not relieved after three serial sublingual NTG tablets or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered along intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 min as needed to relieve symptoms and maintain patient comfort. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory and/or circulatory depression. Meperidine hydrochloride can be substituted in patients who are allergic to morphine.

IV. Anti-Platelet and Anti-thrombotic therapy

Statement 13: Aspirin

It \textbf{IS STRONGLY RECOMMENDED} that aspirin at initial dose of 160-325 mg non-enteric formulation, followed by 80-160 mg daily be administered as soon as possible after presentation and continued indefinitely.

The administration of aspirin has the strongest evidence of clinical benefit in all spectrum of ACS. \textsuperscript{23-24}

Statement 14: ADP receptor antagonists (Clopidogrel, ticlopidine)

It \textbf{IS STRONGLY RECOMMENDED} to start clopidogrel for:

1. Patients in whom an early non-interventional approach is planned in addition to ASA as soon as possible on admission and administered for at least 1 month
2. Patients who are unable to take ASA because of hypersensitivity or major
gastrointestinal intolerance.

3. Patients in whom a PCI is planned and should be continued for at least 12 months in patients who are not at high risk for bleeding.

The trial, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) also provides strong evidence for the addition of clopidogrel to ASA on admission in the management of patients with UA and NSTEMI. The optimal duration of therapy with clopidogrel has not been determined, but the favorable results in CURE were observed over a period averaging 9 months.25-26 (See table 6 or listing and dosages of different anti-thrombotic and anticoagulant drugs)

Table 6: Anti-thrombotic Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapeutic Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral anti-platelet Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td>Initial dose of 160-325 mg non-enteric formulation followed by 80-160 mg/d of an enteric or a non-enteric formulation</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td>75 mg/d; a loading dose of 4-8 tablets (300-600 mg) can be used when rapid onset of action is required</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td>250 mg twice daily; a loading dose of 500 mg can be used when rapid onset of inhibition is required; monitoring of platelet and white cell counts during treatment is required</td>
<td></td>
</tr>
<tr>
<td>Heparins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td></td>
<td>120 IU/kg subcutaneously every 12 h (maximum 10,000 IU twice daily)</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
<td>1 mg/kg subcutaneously every 12 h; the first dose may be preceded by a 30-mg IV bolus</td>
<td></td>
</tr>
<tr>
<td>Nadroparin</td>
<td></td>
<td>86 IU/kg every 12 h</td>
<td></td>
</tr>
<tr>
<td>Unfractionated Heparin (UFH)</td>
<td></td>
<td>Bolus 60-70 U/kg (maximum 5000 U) IV followed by infusion of 12-15 U/kg⁻¹ . h⁻¹ (maximum 1000 U/h) titrated to aPTT 1.5-2.5 times control</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td></td>
<td>2.5 mg subcutaneously daily</td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous Antiplatelet Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td></td>
<td>0.25 mg/kg bolus followed by infusion of 0.125 mcg . kg⁻¹ . min⁻¹ (maximum 10 mcg/min) for 12 to 24 h from the local market</td>
<td></td>
</tr>
<tr>
<td>Eptifibatide</td>
<td></td>
<td>180 mcg/kg IV bolus (second bolus after 10 min for PCI) followed by infusion of 2.0 mcg . kg⁻¹ . min⁻¹ for 72 to 96 h</td>
<td></td>
</tr>
<tr>
<td>Tiroliban</td>
<td></td>
<td>0.4 mcg . kg⁻¹ . min⁻¹ for 30 minutes followed by infusion of 0.1 mcg . kg⁻¹ . min⁻¹ for 48 to 96 h. A high-dose regimen (bolus 25 ug/kg + 0.15 ug/kg/min infusion for 18 h) is tested in clinical trials</td>
<td></td>
</tr>
</tbody>
</table>

It IS STRONGLY RECOMMENDED to discontinue clopidogrel for 5 to 7 days in patients whom elective CABG is planned.

Statement 15: Anticoagulants (Heparins)

It IS STRONGLY RECOMMENDED that anticoagulation with subcutaneous enoxaparine or intravenous unfractioned heparin (UFH) should be added to anti-platelet therapy with ASA and/or clopidogrel.

Heparin exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and Factor Xa. Four large trials have compared LMWH vs UFH. ESSENCE and TIMI IIIB have shown moderate benefit of LMWH over UFH while FRIC and FRAXIS showed unfavorable results for LMWH. The advantage of LMWH is the ease of administration and the absence of a need for monitoring. LMWH stimulated platelets less than UFH hence less frequent association with heparin induced thrombocytopenia. LMWH is more frequently associated with mucosal bleeding but not major bleeding.28-30

During UFH, APTT should be measured at baseline, then 6 hours thereafter. When 2 consecutive APTT values are therapeutic, the measurements may be made every 24h and if necessary, dose adjustments carried out. Serial Hb/Hct & PC measurements are recommended at least daily during UFH therapy. Most of the trials that evaluate the use of UFH in UA/NSTEMI have continued therapy for 2-5 days. The optimal duration of therapy remains undefined.

Enoxaparin may be preferable to UFH as an anticoagulant in patients with UA/NSTEMI, unless CABG is planned within 24 h. This statement was supported by data from that of ESSENCE, TIMI IIb, INTERACT and EVET trials.31-34

Statement 16: Glycoprotein IIbIIa inhibitors

It IS RECOMMENDED to use glycoprotein IIbIIa inhibitors (tirofiban) in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is not planned; or inpatients undergoing PCI with or without clopidogrel administration.

Five trials were conducted using GPIIbIIa inhibitors in UA/NSTEMI. In PRISM and PRISM PLUS, tirofiban appears to be beneficial in high risk patients whether they underwent PCI or not. However, no benefit is observed in low risk patients. In PURSUIT trial, eptifibatide also showed benefit whether they are treated medically or with PCI. However, in GUSTO IV, Abciximab showed no advantage over placebo in medically treated patients where PCI is not planned.35-37
Statement 17: Factor X inhibitor:

It **IS RECOMMENDED** To use fondaparinux, in lieu of enoxaparine, at a dose of 2.5 mg SC once daily in whom a conservative strategy is selected and who have an increased risk of bleeding.

The only selective factor-Xa inhibitor locally available for clinical use is fondaparinux. This is a synthetic pentasaccharide modeled after the anti-thrombin-binding sequence of UFH. It exerts a selective anti-thrombin-mediated inhibition of factor-Xa. Several advantages have been cited for its clinical uses over heparins. It does not induce the formation of heparin-PF4 complexes, hence heparin induced thrombocytopenia (HIT) is unlikely to occur with fondaparinux, therefore, monitoring of platelet count is not necessary. Additionally, the use of Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting time (ACT), pro-thrombin (PT), and thrombin times (TT). This drug is eliminated mainly by the renal route and should not be given if CrCl is lower than 30ml/min.

However, this anticoagulant has propensity for increased rate of catheter-associated thrombosis.38-39

Statement 18: Fibrinolytic therapy

It **IS NOT RECOMMENDED** to use intravenous fibrinolytic therapy in patients with UA or in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block (LBBB).

The failure of IV thrombolytic therapy to improve clinical outcomes in the absence of AMI was clearly demonstrated in the TIMI IIb, ISIS 2, GISSI 1 trials. 32, 40, 41

V. Coronary Revascularization

Statement 19: Early Conservative versus Invasive Strategies

It **IS RECOMMENDED** that an early invasive strategy (as early as possible up to 72 hours) followed by revascularization (PCI or CABG) with any of the following high-risk indicators:

a) Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
b) Elevated cardiac biomarkers (TnT or TnI)
c) New or presumably new ST-segment depression
d) Signs or symptoms of heart failure (HF) or new or worsening mitral regurgitation
e) High-risk findings from noninvasive testing
f) Hemodynamic instability
g) Sustained ventricular tachycardia
h) PCI within 6 months
i) Prior CABG
j) High-risk score (e.g. TIMI, GRACE)
k) Reduced LV systolic function (LVEF less than 40%)

Two different treatment strategies, termed “early conservative” and “early invasive” have evolved for patients with UA/NSTEMI. In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-T segment changes or a strongly + stress tests despite vigorous medical therapy). In the early invasive strategy, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and revascularization if possible within 24-48h after presentation to the ED.

TIMI-IIIb was the first trial to compare strategies of routine catheterization and revascularization in addition to medical therapy and selective use of aggressive treatment 42. The FRISC II and TACTICS trials 43-44 result supports the use of catheterization and revascularization for selected patients with an acute coronary syndrome. The greater benefits derived from percutaneous coronary intervention (PCI) in the TACTICS and FRISC trials can be explained in part by the use of stents and GP-receptor blockers and lower peri-procedural complications.

A conservative strategy may be instituted for patients with low-risk score (e.g., TIMI, GRACE) or according to patient or physician preference in absence of high-risk features

Statement 20: Coronary angiography

It **IS NOT RECOMMENDED** in patients with extensive co-morbidities (e.g. liver or pulmonary failure, cancer), in whom the risks of revascularization are not likely to outweigh the benefits or in patients with acute chest pain and a low likelihood of ACS or in patients who will not consent to revascularization regardless of the findings.

Statement 21: Percutaneous coronary intervention (PCI)

An early invasive PCI strategy **IS RECOMMENDED** for patients with UA/NSTEMI who have no serious co-morbidities (severe hepatic, pulmonary, or renal failure, or active/inoperable cancer) and who have coronary lesions amenable to PCI and any of the high risk features (see statement 19).

PCI (or CABG) is **ALSO RECOMMENDED** for UA/NSTEMI patients with 1-2 vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high risk criteria on non invasive testing.
Statement 22: Coronary artery bypass graft (CABG) surgery

CABG IS RECOMMENDED for patients with significant left main disease and the preferred revascularization strategy for patients with multi-vessel coronary disease, with depressed systolic function (LVEF ≤50%), and diabetes.

VI. Hospital Discharge

Statement 23: It IS RECOMMENDED that the following specific instructions should be given:

a. Lifestyle modification that includes smoking cessation, achievement or maintenance of optimal weight, daily exercise, and diet.

b. Daily exercise of 30 minutes or 5 days per week.

c. Consider referral of patients who are smokers to smoking cessation program or clinic and/or an out-patient cardiac rehabilitation program.

d. Intensive lipid-lowering therapy is strongly recommended by combining dietary interventions with pharmacotherapy using statins, or combination with other lipid-lowering agents to reduce LDLc < 100 mg/dL. Further reduction to less than 70 mg per dL* may be recommended. (* to convert mmol/l to mg/dl: divide values by 0.03).

e. A fibrate or niacin if high-density lipoprotein (HDL) cholesterol is less than 40 mg per dL, occurring as an isolated finding or in combination with other lipid abnormalities.

f. Hypertension control to a blood pressure of less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease.

g. Tight control of hyperglycemia in diabetes. Goal is HbA1c of less than 7%.

h. Antiplatelet Agents/Anticoagulants:

i.1 Aspirin

1. For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 160 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 80 mg to 160 mg daily.

2. In patients for whom the physician is concerned about risk of bleeding, lower-dose 80 mg to 160 mg of aspirin is reasonable during the initial period after stent implantation.

i.2 Clopidogrel

1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for at least indefinitely if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).

2. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.
VIII. References:


30. FRAXIS study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6 day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction. FRAX.I.S. (FRAXiparin in Ischaemic Syndrome). Eur Heart J 1999;20:1553-62.


35. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investiga-
Statement 7: Immediate Surgical Reperfusion

Emergency or urgent CABG IS RECOMMENDED in patients with STEMI in the following circumstances: failed PCI with persistent pain or hemodynamic instability, persistent and recurrent ischemia refractory to medical therapy in patients who are not candidates for PCI or fibrinolytic therapy, cardiogenic shock with left main or severe multivessel disease, and at the time of surgical repair of post-infarct ventricular septal rupture or mitral valve insufficiency.

Statement 8: Hospital management of STEMI

General recommendations for patient with STEMI in Coronary Care Unit

1. STEMI patients should be immediately admitted to a quiet and comfortable environment with qualified personnel, on continuous ECG monitoring, pulse oximetry and has ready access to facilities for hemodynamic monitoring and defibrillation
2. Administer aspirin and beta-blockers in adequate dose to control heart rate and assess the need for intravenous nitroglycerin for control of angina, hypertension, and heart failure

3. When stable for 6 hours, the patient should be reassessed for oxygen need (i.e., saturation of less than 90%) and discontinuation of supplemental oxygen should be considered
4. Nursing care should be provided by individuals knowledgeable in critical care

Statement 9: Risk Stratification of STEMI patients

It IS RECOMMENDED that STEMI patients should be stratified into high-risk patients and low-risk patients:

Statement 10: Hemodynamic Assessment

It IS RECOMMENDED that high-risk patients with mechanical complications of STEMI and/or progressive hypotension should have pulmonary artery catheter and intra-arterial pressure monitoring. Intra-aortic balloon counter-pulsation and early revascularization should be considered.

Statement 11: Management of Arrhythmias after STEMI

The following statements are the general recommendations of Management of Arrhythmias after STEMI:

1. Ventricular Fibrillation (VF) or pulseless VT: Immediate cardioversion with 120 J to 200 J
62

Statement 13: Statement on Implantable Cardioverter Defibrillator

It IS RECOMMENDED that Implantable Cardioverter Defibrillator be placed in the following conditions:

1. Patients with VF or hemodynamically sustained VT more than 2 days after STEMI (provided that VF or VT is not judged to be due to transient or reversible ischemia or reinfarction)
2. Patients with VF or sustained VT more than 48 hours after STEMI whose STEMI occurred at least 1 month previously, with an LVEF between 0.31 and 0.40, and have inducible VF or VT on electrophysiologic testing.

Statement 14: Anticoagulant Therapy

It IS RECOMMENDED that patients undergoing reperfusion therapy with fibrinolytics receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of the index hospitalization, preferably up to 8 days.

Statement 15: Antiplatelet Therapy

It IS RECOMMENDED that Clopidogrel 75 mg per day orally be added to aspirin in patients with STEMI and maintained for at least 14 days.

Statement 16: Beta Blocker therapy

It IS STRONGLY RECOMMENDED that beta blocker therapy be started within 24 hours of STEMI in the absence of contraindication (frank heart failure, hypotension, heart block, active asthma or reactive airway disease, increased risk of cardiogenic shock i.e age more than 70, SBP less than 120 mmHg, heart rate greater than 110, Killips greater than class I and in the presence of concomitant hypertension or uncontrolled blood pressure)

Statement 17: Anti-cholesterol Agents: Statins

High dose statins MAY BE RECOMMENDED within 1st 24 hours of admission in the absence of contraindication (such as known allergy, active liver disease).

Statement 18: Angiotensin Converting Enzyme inhibitors (ACE-I)

It IS STRONGLY RECOMMENDED that ACE-I be started within 24 hours in patients with anterior infarction, pulmonary congestion or left ventricular ejection fraction (LVEF) of <= to 40% and continued indefinitely among patients with LVEF <= to 40%, hypertension, diabetes or chronic kidney disease (CKD).
I. Recommendations on Initial Patient Evaluation:

Statement 1: Pre hospital recognition

It IS RECOMMENDED that patients with symptoms of chest discomfort, shortness of breath, diaphoresis, nausea, weakness be immediately brought to the nearest emergency room of a hospital.

Morbidity and mortality from ST elevation myocardial infarction (STEMI) can be reduced by early recognition of symptoms and timely medical consultation and institution of treatment. Patients and their relatives should be given information on how to recognize signs and symptoms of STEMI and should be informed of the urgency of seeking medical attention.

If the patient has been previously prescribed nitroglycerin, it is recommended that the patient be advised to take ONE nitroglycerin dose sublingually for chest discomfort. If the symptoms are unimproved or is worsening after five minutes, it is recommended that the patient seek medical consult without further delay. Taking additional doses of nitroglycerin or other medications is no longer recommended as to avoid further delay in seeking medical attention.

Statement 2: Initial evaluation at the Emergency Room (ER)

It IS STRONGLY RECOMMENDED that a detailed history taking, physical examination and a 12 lead ECG be taken within 10 minutes of arrival at the ER. The objective of initial evaluation is for the physician to rapidly and reliably diagnose STEMI and to determine the patient’s eligibility for reperfusion therapy. The patient should be placed on a cardiac monitor immediately, with emergency resuscitation equipment including a defibrillator, nearby.

The targeted history taken in the ER should be detailed enough to establish the probability of STEMI but should be obtained rapidly so as not to delay reperfusion therapy. The history should focus on the chest discomfort and associated symptoms, considering age and sex related differences in presentation. The chest discomfort is often described as constricting or like a sensation of something heavy on the chest. The location is usually substernal but may originate or radiate to areas such as the neck, jaw, interscapular area, upper extremities and epigastrium. The discomfort may wax and wane and typically last longer than 30 minutes. Associated symptoms of diaphoresis, nausea and vomiting, light headedness as well as weakness and fatigue may occur. Women generally present at an older age than men. Elderly patients are less likely to complain of chest discomfort and more often present with shortness of breath, nausea or syncope.

Statement 19: Angiotensin receptor blockers (ARB)

ARB IS RECOMMENDED in patients who are intolerant to ACE-I and have clinical or radiological signs of heart failure or EF less than 40%.

Statement 20: Renin-Angiotensin-Aldosterone System Blockers: Aldosterone Blockade

It IS RECOMMENDED to use an aldosterone blocker (spironolactone) in post STEMI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of beta blocker and ACE inhibitor who have LVEF<= 40% and have either diabetes or heart failure.

Statement 21: Glucose control therapy

It IS RECOMMENDED that Insulin IV, ideally via infusion pump be used to achieve optimum sugar level among patients with STEMI and complicated courses.

Statement 22: Metabolic Modulators

(trimetazidine, nicorandil)
It IS NOT RECOMMENDED to give Trimetazidine among patients with STEMI undergoing thrombolysis.

Statement 23: Cardiac Rehabilitation

It IS STRONGLY RECOMMENDED that all patients with ST segment elevation undergo cardiac rehabilitation.

Statement 24: Hospital discharge and post STEMI risk stratification: Timing of Hospital Discharge

If patient have undergone reperfusion therapy with no significant arrhythmias, recurrent ischemia or congestive heart failure, patient can be safely discharged in less than 5 days.

Statement 25: Exercise Testing

Exercise testing IS RECOMMENDED either before discharge (submaximal), early after discharge (2-3 wks) or late after discharge( 3-6wks) for prognostic, activity prescription, evaluation of medical therapy.
Prior episodes of myocardial ischemia, infarction, percutaneous coronary intervention (PCI) or bypass surgery, as well as co morbid illnesses including hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding and clinical cerebrovascular disease should be sought. Severe tearing pain radiating to the back associated with dyspnea or syncpe without ECG changes indicative of myocardial ischemia or infarction should raise the possibility of aortic dissection (see table 1 for differential diagnosis for Acute Myocardial Infarction (AMI)). However, previous bleeding problems, history of ulcer disease, cerebral vascular accidents, and unexplained anemia should be sought since they can be exacerbated with the use of fibrinolytics, anti-platelets and antithrombins in the treatment of STEMI.

A brief physical examination should be performed to aid in the diagnosis and assessment of the extent, location and presence of complications of STEMI. A limited neurologic examination to look for evidence of prior stroke or cognitive deficits should be performed before administration of fibrinolytic therapy.

Table 1: Differential Diagnosis for AMI

<table>
<thead>
<tr>
<th>Life Threatening:</th>
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<tbody>
<tr>
<td>Aortic Dissection</td>
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<tr>
<td>Pulmonary embolus</td>
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<tr>
<td>Perforating Ulcer</td>
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<tr>
<td>Tension Pneumothorax</td>
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<tr>
<td>Boerhave Syndrome (Esophageal rupture with mediastinitis)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Other Cardiovascular and Non Ischemic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericarditis</td>
</tr>
<tr>
<td>Atypical Angina</td>
</tr>
<tr>
<td>Early repolarization</td>
</tr>
<tr>
<td>Wolff-Parkinson-White Syndrome</td>
</tr>
<tr>
<td>Deeply Inverted T waves suggestive of central nervous system lesion or apical hypertrophy</td>
</tr>
<tr>
<td>LV hypertrophy with strain</td>
</tr>
<tr>
<td>Brugada Syndrome</td>
</tr>
<tr>
<td>Myocarditis</td>
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<tr>
<td>Hyperkalemia</td>
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</tbody>
</table>

An ECG should be taken and shown to an experienced physician within 10 minutes of arrival in the ER. If STEMI is present, a decision whether the patient will be treated with fibrinolytic therapy or PCI should be made within 10 minutes. If the initial ECG is not diagnostic and the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECG’s at 5-10 minute interval or continuous ST segment monitoring should be done.

**Statement 3: ECG**

It IS RECOMMENDED that patients presenting with chest discomfort and ECG finding of at least 0.1 mV ST segment elevation in two contiguous leads and without any contraindications receive reperfusion therapy either primary PCI (in hospitals with PCI capability) or with thrombolysis (in hospitals without PCI capability).

The presence of at least 0.1 mV ST segment elevation in two contiguous ECG leads identifies patients who benefit from reperfusion therapy. Fibrinolytic therapy has no evidence of benefit for patients with normal ECG or non specific changes and with some evidence of harm for patients with ST segment depression only. Patients presenting with marked ST segment depression in leads V1 to V4 accompanied by tall R waves in the right precordial leads and upright T waves may have true posterior infarction and may also benefit from fibrinolytic therapy. Patients with new or presumably new LBBB are at high risk when presenting with presumed MI. It has been suggested that these patients be approached with a plan to rule in MI using 1 of 3 ECG criteria that provide independent diagnostic value. These are: 1) ST elevation...
Aspirin at a dose of 160 to 325 mg should be chewed by the patient who has not yet taken aspirin before presentation with STEMI. More rapid buccal absorption occurs with non-enteric-coated aspirin formulations. The Second International Study of Infarct Survival (ISIS 2) have shown conclusively the efficacy of aspirin alone (ARR 2.4%, RRR 23% in 35 day mortality) and combined with streptokinase (ARR 5.2%, RRR 42%) in the treatment of evolving acute MI. Aspirin should not be given in those with hypersensitivity to salicylates, instead clopidogrel or ticlopidine should be given.

II. RECOMMENDATIONS ON HOSPITAL CARE

Statement 5: Thrombolysis or fibrinolytic Therapy

STEMI patients presenting to a hospital without facilities for primary percutaneous coronary intervention (PCI) IS RECOMMENDED to undergo immediate thrombolysis unless contraindicated with a door to needle time < 30 minutes as goal.

The cardinal goal of treatment for all STEMI patients is to consider reperfusion therapy and to initiate such therapy as quickly as possible in patients presenting at the emergency room < 12 hours from onset of chest pain. The choice of reperfusion therapy will depend on the clinical presentation of the patient, the availability of resources and expertise, cost consideration and the patient’s preference. Thrombolysis is recommended if the clinical presentation is < 3 hours from onset of chest pain, there is lack of access to a skilled PCI laboratory, or a delay is expected of invasive strategy (prolonged transport time or catheterization laboratory occupied).

The clinician should assess the adequacy of reperfusion by monitoring the pattern of ST elevation (reduction of at least 50% of the initial ST-segment elevation injury pattern), cardiac rhythm and clinical symptoms over 90 minutes after initiation of thrombolytic therapy.

Contraindications and cautions for fibrinolysis in STEMI: (Viewed as advisory for clinical decision making and may not be all-inclusive or definitive)

Absolute Contraindications:
Any prior intracranial hemorrhage
Known structural cerebral vascular lesion (e.g. arterio-venous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months except acute ischemic stroke within 3 hours
Comfortable environment with qualified personnel, on continuous ECG monitoring, pulse oximetry and has ready access to facilities for hemodynamic monitoring and defibrillation

2. It is recommended to administer aspirin and beta-blockers in adequate dose and assess the need for intravenous nitroglycerin for control of angina, hypertension, and heart failure

3. It is recommended that patient should be reassessed for oxygen need (i.e., saturation of less than 90%) if stable for 6 hours, and discontinuation of supplemental oxygen should be considered

4. Nursing care should be provided by individuals knowledgeable in critical care

Statement 8: Risk Stratification

It is RECOMMENDED that STEMI patients be stratified into high-risk patients and low-risk patients:

High-risk patients are those with recurrent ischemia, reinfarction, life-threatening arrhythmias (sustained ventricular tachycardia or fibrillation, high-degree atrio-ventricular block, or major supraventricular arrhythmias), or clinical evidence of pump dysfunction (rales or hypotension); those with mechanical complications of infarction (cardiogenic shock, ventricular septal defect, acute mitral regurgitation, and free-wall rupture)

Low-risk patients: absence of recurrent ischemia, heart failure, or hemodynamically compromising arrhythmias. Low-risk patients who have undergone successful PCI be admitted directly to telemetry or regular room in close supervision for post PCI care rather than in CCU. Further, low risk STEMI patients who demonstrate 12-24 hours of clinical stability should be transferred out of CCU.

Statement 9: Hemodynamic Assessment

It is RECOMMENDED that high-risk patients with mechanical complications of STEMI and/or progressive hypotension have pulmonary artery catheter and intra-arterial pressure monitoring. Intra-aortic balloon counter-pulsation and early revascularization should be considered.

Statement 10: Management of Arrhythmias after STEMI

The following statements are the general recommendations of Management of Arrhythmias after STEMI:

1. Ventricular Fibrillation (VF) or pulseless VT: Unsynchronized electric shock with initial shock energy of 200 J; if unsuccessful, a second shock of 200-300

Relative Contraindications:

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP greater than 180 mmHg or DBP greater than 110 mmHg) *
- History of prior ischemic stroke greater 3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks)
- Recent (within 2-4 weeks) internal bleeding
- Non compressible vascular punctures
- For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer disease
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

* Could be an absolute contraindications in low-risk patients with MI

Statement 6: Catheter-based therapy

It is RECOMMENDED that STEMI patients presenting to a PCI capable hospital and with an available skilled operator be treated with primary PCI within 90 minutes of first medical contact.

Generally preferred also in the following conditions:

1. PCI capable laboratory available with surgical back-up
2. High risk patient (cardiogenic shock, pulmonary edema)
3. Contraindication to thrombolysis
4. Late presentation (> 3 hours from onset of chest pain)
   - Interhospital transfer to PCI capable hospital is recommended for patients presenting with cardiogenic shock, hemodynamic instability and patients with failed thrombolysis for rescue PCI purposes.

Statement 7: General recommendations on hospital management of STEMI

General recommendations for patient with STEMI in Coronary Care Unit

1. STEMI patients is recommended to be immediately admitted to a quiet and comfortable environment with qualified personnel, on continuous ECG monitoring, pulse oximetry and has ready access to facilities for hemodynamic monitoring and defibrillation

2. It is recommended to administer aspirin and beta-blockers in adequate dose and assess the need for intravenous nitroglycerin for control of angina, hypertension, and heart failure

3. It is recommended that patient should be reassessed for oxygen need (i.e., saturation of less than 90%) if stable for 6 hours, and discontinuation of supplemental oxygen should be considered

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The following statements are the general recommendations of Management of Arrhythmias after STEMI:

1. Ventricular Fibrillation (VF) or pulseless VT: Unsynchronized electric shock with initial shock energy of 200 J; if unsuccessful, a second shock of 200-300
It IS RECOMMENDED that Implantable Cardioverter Defibrillator be placed in the following conditions:

1. Patients with VF or hemodynamically sustained VT more than 2 days after STEMI (provided that VF or VT is not judged to be due to transient or reversible ischemia or reinfarction)
2. Patients with VF or sustained VT more than 48 hours after STEMI whose STEMI occurred at least 1 month previously, with an LVEF between 0.31 and 0.40, and have inducible VF or VT on electrophysiologic testing.

III. RECOMMENDATIONS ON DRUG THERAPY

Statement 13: Anticoagulant Therapy

It IS RECOMMENDED that patients undergoing reperfusion therapy with fibrinolytics receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of the index hospitalization, preferably up to 8 days.

Anticoagulant therapy is beneficial in patients with STEMI, and there is benefit in more prolonged anticoagulant therapy. The mechanism of benefit may be multifactorial and may be due to prevention of rethrombosis of the infarct artery and prevention of rebound increase in events after abrupt discontinuation of unfractionated heparin (UFH).

The following anticoagulant regimens have established efficacy:

a. UFH (initial intravenous bolus 60 U per kg [maximum 4000 U]) followed by an intravenous infusion of 12 U per kg per hour (maximum 1000 U per hour) initially, adjusted to maintain the activated partial thromboplastin time (PTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds)

b. On low molecular weight heparin:

a. Enoxaparin can be given provided the serum creatinine is less than 2.5 mg per dL in men and 2.0 mg per dL in women

For patients < 75 years of age, an initial 30 mg intravenous bolus is given, followed 15 minutes later by subcutaneous injections of 1.0 mg per kg every 12 hours

For patients at least 75 years of age, the initial intravenous bolus is eliminated
Statement 14: Antiplatelet therapy

It **IS RECOMMENDED** that Clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI and maintained for at least 14 days.

The COMMIT-CCS-2 randomized 45,852 patients within 24 hours of suspected AMI to 75 mg clopidogrel daily for up to 4 weeks versus placebo in addition to 162 mg of aspirin daily. The composite primary endpoint of death, reinfarction, or stroke was reduced from 10.1% in the placebo to 9.2% in the clopidogrel group. (OR 0.91 [95% CI 0.86 to 0.97]) 9

The CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28) study randomized 3491 patients receiving fibrinolytic therapy within 12 hours of STEMI to clopidogrel (300 oral loading dose followed by 75 mg oral daily dose) or placebo. There was a reduction in the primary composite endpoint of an occluded infarct artery or recurrent MI before angiography from 21% in the placebo to 15% in the clopidogrel group. (OR 0.64 [95% CI 0.53 to 0.76]; p less than 0.001. This benefit has been thought to be primarily due to prevention of infarct related artery reocclusion. The rate of TIMI major bleeding was 1.7% in the placebo and 1.9% in the clopidogrel group (p=0.80). 4

There is no available data on long term therapy with clopidogrel in STEMI but extrapolating from experience with UA/NSTEMI suggests that it can be useful.

It is reasonable to administer an oral loading dose of 300 mg of clopidogrel in patients less than 75 years old.

Statement 15: Beta Blocker therapy

It **IS STRONGLY RECOMMENDED** that beta blocker therapy be started within 24 hours of STEMI in the absence of contraindication (**frank heart failure, hypotension, heart block, active asthma or reactive airway disease, increased risk of cardiogenic shock** i.e age more than 70, **SBP less than 120 mmHg, heart rate greater than 110, Killips greater than class I and in the presence of concomitant hypertenion or uncontrolled blood pressure**)

Use of beta blocker should also be considered and carefully titrated during the latter phase of STEMI among patients who initially presented contraindications to its use within the 24 hours

The use of beta blocker in patients after myocardial infarction has been proven to increase survival, decrease magnitude of extension and associated complications even when used early in the fibrinolytic era (ISIS-I, MIAMI, TIMI II). 5-7 These findings were later refuted by GUSTO I which revealed no benefit in survival among patients given early IV atenolol. 8

The COMMIT/CCS-2 trial using intravenous and high dose oral metoprolol (200 mg/day) given at day 0-1 of myocardial infarction has shown lesser episodes of re-infarction and ventricular fibrillation but with significantly higher episodes of cardiogenic shock. Because of these findings and lack of benefit of early (day 0-1) oral beta blocker use, careful dose titration among selected patients should be exercised when giving beta blocker early in the course of myocardial infarction. 9

Use of beta blocker in the latter course (from day 2) among patients with no contraindication has been proven to increase survival and major adverse cardiac events (MACE).

Locally, we have no available IV metoprolol in the market hence, oral route sufficed in our administration of beta blockers.

Statement 16: Anti-cholesterol agent: Statins

High dose statins **MAY BE RECOMMENDED** within 1st 24 hours of admission in the absence of contraindication (**such as known allergy, active liver disease**)

The use of statins as secondary prevention in patients who survived a myocardial infarction is no longer of question. Its use in the early phase of acute coronary syndrome has also proven to confer some benefit as seen in the study Myocardial
Statement 17: Angiotensin Converting Enzyme inhibitors (ACE-I)

It IS STRONGLY RECOMMENDED that ACE-I be started within 24 hours in patients with anterior infarction, pulmonary congestion or left ventricular ejection fraction (LVEF) of $\leq$ 40% and continued indefinitely among patients with LVEF $\leq$ 40%, hypertension, diabetes or chronic kidney disease (CKD).

ACE-I MAY BE RECOMMENDED among lower risk patients (S/P revascularization procedures, controlled cardiovascular risk factors, normal ejection fraction recovering from STEMI).

Several studies have shown benefit in starting ACE inhibition in acute STEMI within the 1st 24 hours of the event. In ISIS-4 study, it resulted to a 7% relative risk reduction in the 5-week mortality of AMI patients who were given captopril vs placebo, the benefit was mostly noted in those patients having anterior infarction. In GISSI-3 trial, administration of lisinopril to patients with STEMI or NSTEMI resulted to a decreased mortality in 6 weeks when compared to active control. In both studies the survival benefit was significant during the 1st week of the AMI hence the emphasis on early treatment. Further, in the report submitted by Chinese Cardiac Study group which enrolled more than 16,000 patients also showed survival benefit in the early use of captopril in AMI patients. A meta-analysis on early ACE inhibition conducted in both major and smaller trials also resulted to 6.5% odds reduction in mortality. However, one trial that did not show any improvement in survival is the CONSSENSUS II study which randomized AMI patients to IV enalapril or placebo. IV enalapril resulted to hypotension especially among the elderly which led to premature discontinuation of the study due to safety issues. In summary, there is enough evidence to support initiating ACE-I in AMI in the absence of contraindications (hypotension, bilateral renal artery stenoses, significant renal failure and known allergy). Patients should be started on small doses and titrated to optimal levels (captopril 50 mg BID in ISIS-4 and lisinopril 10 mg OD in GISSI-3) in the absence of adverse reactions. The subsets of patients in whom ACE-inhibitors are most beneficial are those with heart failure, anterior infarction and low LVEF. The data is equivocal among lower risk patients although no harm has been documented.

Statement 18: Angiotensin receptor blockers (ARB)

ARB IS RECOMMENDED in patients who are intolerant to ACE-I inhibitors and have clinical or radiological sign of heart failure or EF less than 40%.

ARB IS ALSO RECOMMENDED in patients who are intolerant to ACE inhibitors and have hypertension.

ARB in combination with ACE inhibitors may also be recommended in those patients with systolic dysfunction and heart failure. Compared to ACE inhibitors, ARB’s role in acute MI is not well established hence in these guidelines, the use of ARB’s is only recommended among patients who are intolerant to the former.

Statement 19: Renin-Angiotensin-Aldosterone System Blockers: Aldosterone Blockade

It IS RECOMMENDED to use aldosterone blockade (spironolactone) in post STEMI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of beta blocker and ACE inhibitor who have LVEF $\leq$ 40% and have either diabetes or heart failure.

Statement 20: Glucose control therapy

It IS RECOMMENDED that insulin IV, ideally via infusion pump should be used to achieve optimum sugar level among patients with STEMI particularly with complicated hospital course.

It is prudent to administer IV insulin among patients with STEMI during the first 24 to 48 hours to achieve optimum blood sugar level even among patients with uncomplicated course. The surge of catecholamines in acute STEMI increases glucagon and cortisol which in turn decreases insulin sensitivity contributing to impaired glucose utilization and increased fatty oxidation. Free fatty acid concentration and their metabolite increase potentiating ischemic injury through myocardial toxicity, increased oxygen demand and direct inhibition of glucose utilization. Insulin promotes glucose oxidation, decreases free fatty acids increased energy levels (ATP) and promotes fibrinolytic property in STEMI.

Statement 21: Metabolic Modulators (trimetazidine, nicorandil)

It IS NOT RECOMMENDED to give Trimetazidine among patients with STEMI undergoing thrombolysis.

Trimetazidine, a metabolic agent with anti-anginal properties lessens ischemic
injury and improves cardiac performance during ischemia through reduction in fatty acid oxidation and stimulation of glucose oxidation. However, its anti-anginal efficacy noted in numerous small randomized trials was mostly conducted in chronic stable patients. Trimetazidine may be beneficial among non–thrombolysed STEMI patients.

Nicorandil is a KATP channel opener that has hemodynamic and cardioprotective effects noted to be useful in a study conducted in patients with UA/NSTEMI. In a pilot double-blind, placebo-controlled study of 245 patients with UA, the addition of nicorandil to conventional treatment significantly reduced the number of episodes of transient myocardial ischemia (mostly silent) and of ventricular and supraventricular tachycardia. Further evaluation of this class of agents is underway.

IV. RECOMMENDATIONS ON POST MI EVALUATION:

Statement 22: Cardiac Rehabilitation

It IS STRONGLY RECOMMENDED that all patients with ST segment elevation undergo cardiac rehabilitation.

Cardiac rehabilitation is a comprehensive, long-term program involving medical evaluation, prescription of exercise program, cardiac risk factor modification, education and counseling. Cardiac rehabilitation should start as early as possible. A substantial proportion of coronary heart disease (CHD) deaths occur in people already known to have the disease. Measures to influence the course of already recognized CHD might help significantly to reduce the total attributable mortality. Rehabilitation goals include all secondary prevention goals. This is defined as an effort towards risk factor reduction designed to lessen the chance of a subsequent cardiac event and to slow and perhaps stop progression of the disease process.

Rest, Exercise and Exercise Training

Rest

Physical rest or bed rest is necessary in patients with heart failure. Passive mobilization exercises are carried out to prevent untoward effects resulting from prolonged bed rest and to decrease the risk of venous thrombosis.

Exercise

In order to prevent muscle de-conditioning, a stable patient should be advised on how to carry out daily physical activities that do not induce symptoms. Strenuous or isometric exercises, competitive and tiring sport should be discouraged. If the patient is employed, their work tasks must be assessed and advised given on whether they can be continued.

Exercise Training

Exercise training programs are encouraged in stable patients. Some randomized trials have shown that regular exercise can safely increase physical capacity by 15-25%, improve symptoms and perception of quality of life in patients with stable class II and III heart failure.

All CHD patients should have a planned preventive measure as part of the usual care. The following are guidelines for long term management:

1. Smoking cessation
2. To maintain/achieve the ideal body weight
3. To educate patient on a diet low in saturated fat and cholesterol. A patient with a low density lipoprotein cholesterol greater than 100 mg/dl despite diet should be given drug therapy with the goal of reducing LDL to less than <70 mg/dL.
4. Blood pressure control
5. Sugar control
6. Stress management
7. Exercise prescription to help increase exercise tolerance

Statement 23: Hospital discharge and post STEMI risk stratification: Timing of Hospital Discharge

If patient have undergone reperfusion therapy with no significant arrhythmias, recurrent ischemia or congestive heart failure, patient can be safely discharged in less than 5 days.

Statement 24: Exercise Testing

Exercise testing IS RECOMMENDED either before discharge (submaximal), early after discharge (2-3 wks) or late after discharge (3-6wks) for prognostic, activity prescription, evaluation of medical therapy.

Sub-maximal protocol requires that patient exercise until symptoms of angina appear, ECG changes of ischemia is seen or 5mets is reached. Exercise testing is not indicated in the following conditions:

1. Patients with severe co-morbidity likely to limit life expectancy and/or candidacy for revascularization.
2. Patients in heart failure, cardiac arrhythmia or non-cardiac condition that limit their ability to exercise.
V. ALGORITHM

Chest discomfort/pain

Is chest discomfort/pain relieved after 1 dose of SL NTG? NO

Is the ECG suggestive of STEMI? * YES

Dynamic ST-T wave changes, T wave inversion, normal

Go to PHA UA/NSTEMI guidelines

Is the receiving hospital PCI capable? NO

Is thrombolysis immediately available? NO

Transfer to a tertiary medical center

Primary PCI with a door to balloon time of 90 minutes

Proceed with Thrombolysis with a door to needle time of 30 minutes

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Is chest discomfort/pain relieved after 1 dose of SL NTG? NO

Is the ECG suggestive of STEMI? * YES

Dynamic ST-T wave changes, T wave inversion, normal

Go to PHA UA/NSTEMI guidelines

Is the receiving hospital PCI capable? NO

Is thrombolysis immediately available? NO

Transfer to a tertiary medical center

Primary PCI with a door to balloon time of 90 minutes

Proceed with Thrombolysis with a door to needle time of 30 minutes

*Initial management of AMI should be instituted: supplemental oxygen during the first 6 hours; aspirin 160-325mg tablet to be chewed; nitrates sublingual or IV; morphine 2-4mg IV for chest pain relief; anti-platelets and anticoagulants; beta-blockers if no contraindication; ACE-I

VI. REFERENCES:


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